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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,677	06/15/2005	Hiroshi Hirai	2005_0629A	4373

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,677	HIRAI ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *8 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *April 26, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group 2a in the reply filed on 5/21/2007 is acknowledged. The traversal is on the ground(s) that claim 1 represents a single inventive concept. This is not found persuasive because variable X can be four different groups, NH, S, O, or CH_2. Even though the classification for each of the molecules can remain the same (class 540, subclass 476), a different structural query is required for each variation of X. In addition, variable Y is two groups, O or NR'. Thus, at least 8 different cores exist for formula I of claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed April 26, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. No copies of the foreign documents have been submitted.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of the following cancers that are controlled by cyclin-dependent kinase 4: glioma (blastoma), breast, lung, gastrointestinal, endometrial, leukemia,

head and neck, liver, ovary or testicular, and mesothelioma, and the following cancers associated with CDK6: glioma (blastoma), lymphoma, and other sarcomas, does not reasonably provide enablement for treatment of pituitary gland cancer, pancreatic cancer, bladder cancer, prostate cancer, and melanomas.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants have shown that the prepared compounds are able to inhibit cyclin-dependent kinase (CDK) 4 (pages 70-73) and CDK6 (page 74, table 2). Malumbres (*Nature Reviews: Cancer*, **2001**, *1(3)*, 222-231) shows that CDK4 is associated in over 90 % of the following types of cancers: glioma (blastoma), breast, lung, gastrointestinal, endometrial, leukemia, head and neck, liver, and ovary or testicular (figure 2, page 226). Fischer et al. (*Expert Opinion on Investigational Drugs*, **2003**, *12(6)*, 955-970) shows that CDK4 inhibition is able to treat mesothelioma. Malumbres also shows in figure 2 that CDK6 inhibition is linked to treatment of the following types of cancers: glioma (blastoma), lymphoma, and other sarcomas. Malumbres shows that CDK4 and CDK6 are not linked with the treatment of pituitary gland cancer, pancreatic cancer, bladder cancer, prostate cancer, and melanomas.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to macrocyclic compounds having at least 5 rings as part of the core structure. Thus, the claims taken together with the specification imply these compounds are able to treat cancer.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

It is known in the prior art that inhibition of various CDKs is linked to the treatment of different cancers (Fischer et al., see above).

(5) The relative skill of those in the art:

One of ordinary skill in the art is knowledgeable in the preparation of these compounds and the *in vitro* testing against cyclin-dependent kinases.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for compounds of claim 1 for the inhibition of CDK4 and CDK6.

However, the specification does not provide guidance for the inhibition of any other CDKs. Only compounds 11, 51, and 134 were tested for CDK6 activity (page 74, table 2). These compounds represent a limited scope of the prepared compounds where variable R is hydrogen or a substituted methyl-piperadine. What happens when variable R is changed to an electron-withdrawing group? Will the compound still inhibit CDK6? Applicants show that a broad representation of example compounds (variable R is shown as electron-donating and withdrawing groups) inhibit CDK4, so treatment of cancers that are linked to CDK4 are enabled.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claim 17 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

5. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds 1-146 that fall within the elected group (where one, variables B_1 through B_5 are C or two, B_3 is N and B_1, B_2, B_4, and B_5 are C, and Y is O), does not reasonably provide enablement for other possibilities of variables B_1 through B_5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants show the preparation of compounds in the specification that fall within the elected group. In these compounds, variable B_3 is N and B_1, B_2, B_4, and B_5 are C or B_1 through B_5 are C and Y is O. However, applicants do not show the preparation of compounds where variables B_1 through B_5 are other combinations and Y is S. Variables B_1 through B_5 can be CH, CR_0, N, or O. The synthetic schemes shown on page 54 make only compounds where variables B_1 through B_5 are C or N. The synthetic schemes involved are not shown how they can be adopted to make compounds where any one of B_1 through B_5 is oxygen, nor where each B is N. Applicants have also not shown any examples schemes where Y equals S.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature

of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to macrocyclic compounds composed of quinazoline rings and indazole rings that are linked by a 5-atom chain. The scope of the claims is such that the B_1 through B_5 linker can be many possibilities because each B variable is 4 different groups.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Compounds of claim 1 are not known in the art much less for uses relied on herein.

(5) The relative skill of those in the art:

One of ordinary skill in the art is a chemist familiar with macrocyclic coupling reactions.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for compounds of claim 1 where one, variables B_1 through B_5 are C or two, B_3 is N and B_1, B_2, B_4, and B_5 are C, and Y is O.

However, the specification does not provide guidance for other combinations of variables B_1 through B_5 and Y equaling S.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-3 and 15-16 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 contains the phrase "amount of one or more kinds of the quinoxalinone derivative according to claim 1 as an active ingredient". This phrase is unclear to how many derivatives of quinoxalinone of claim 1 are being administered to a patient. What is the optimum ratio of one derivative to another? What derivatives are being administered together? Are the compounds administered simultaneously or consecutively?

8. Claims 1-7 and 9-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "ester thereof" for each of these claims renders the structure indefinite. The point of attachment for the ester to the parent compound is not specified. None of the prepared compounds are esters themselves, and therefore it is difficult to determine what is meant by an ester of the claimed compounds.

Claim Objections

9. Claims 1 and 11 are objected to because of the following informalities: they contain non-elected subject material. Appropriate correction is required.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Noble Jarrell /NJ/

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